Appendix 2

Appendix 2

Clinical Protocol 936-9213

"Determination of the Anticaries Efficacy of a Fluoride Mouthrinse Using an Intraoral Caries Test "

Consumer Healthcare Research and Development
Warner Lambert Company

CLINICAL PROTOCOL

PROTOCOL 936-9213

Determination of the Anticaries Efficacy of a Fluoride Mouthrinse Using an Intraoral Caries Test

Principal Investigator: Dr. Domenick Zero

Oral Health Research Institute, Indiana University
415 Lansing Street, Indianapolis, Indiana 46202-2876

May 10, 2000

CONFIDENTIAL

PROTOCOL FOR CONSUMER HEALTHCARE RESEARCH AND DEVELOPMENT CLINICAL TRIAL

PROTOCOL 936-9213

TITLE: Determination of the Anticaries Efficacy of a Fluoride Mouthrinse Using an Intraoral Caries Test

Consumer Healthcare R&D Colleagues	**SIGNATURE**	**DATE**
Jane Zhang, Ph. D Scientist Oral Care Technology Development	_____	_____
Scott Harper, Ph. D Section Director Oral Care Technology Development	_____	_____
Arnold Olshan, MS Clinical Research Associate Dental Affairs	_____	_____
Michael L. Barnett, DDS Senior Director Dental Affairs/Oral Care Technology Development	_____	_____
Kon K. Fung, Ph. D Senior Director Statistics and Data Management	_____	_____
Judith M. Sills, Pharm D. Senior Director U.S. Regulatory Affairs and Global Safety	_____	_____

CONSUMER HEALTHCARE RESEARCH AND DEVELOPMENT
DIVISION OF WARNER-LAMBERT COMPANY
Oral Care Technology Development
170 Tabor Road
Morris Plains, NJ 07950
Phone: 973-385-3345
Fax: 973-385-4300

The above signed confirm herewith to have read and understood this trial protocol and attached appendices, furthermore, to accomplish this study according to the protocol and the Good Clinical Practice guidelines, as well as local regulations, and to accept respective revisions conducted by authorized personnel of Consumer Healthcare Research and Development and by competent authorities.

PROTOCOL FOR CONSUMER HEALTHCARE RESEARCH AND DEVELOPMENT CLINICAL TRIAL

PROTOCOL 936-9213

TITLE: Determination of the Anticaries Efficacy of Fluoride Mouthrinse Using an Intraoral Caries Test

TIME PERIOD AND NUMBER OF SUBJECTS

A.	Anticipated Starting Date of Study:	August 1, 2000
B.	Anticipated Completion Date	December 31, 2000
C.	Anticipated Number of Sites:	One
D.	Number of Subjects to Start Study:	42
E.	Number of Subjects to Complete Study:	36

PRINCIPAL INVESTIGATOR **SIGNATURE** **DATE**

Domenick Zero, DDS, MS _____ _____

Oral Health Research Institute
Indiana University
415 Lansing Street
Indianapolis, IN 46202-2876

INSTITUTIONAL REVIEW BOARD/ETHICS COMMITTEE:

Indiana University
Research and Sponsored Programs
620 Union Drive, Rm. 618
Indianapolis, IN 46202-5167

LABORATORY:
Oral Health Research Institute
Indiana University
415 Lansing Street
Indianapolis, IN 46202-2876

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1 STUDY OBJECTIVE

The objective of this study is to determine the anticaries efficacy of a fluoride mouthrinse using an intraoral caries test model. The primary efficacy variable will be mineral content change in incipient enamel lesions using microhardness analysis (Featherstone and Zero, 1992, Koulourides, etc, 1974). The secondary efficacy variable will be fluoride uptake determined using microdrill biopsy and microdiffusion analysis (Mobley, 1981).

2 SUMMARY OF STUDY DESIGN

This observer-blind, controlled crossover study will use an intraoral caries test (ICT) model. Mineral content change, assessed by Percent Surface Microhardness (%SMH) recovery, and fluoride uptake in incipient enamel lesions will be determined after use of the test formulation, a positive control rinse, and a negative control rinse. The intraoral buccal flange partial denture appliance to be used in this study has been used previously by the principle investigator (Zero, 1995).

The test product will be a fluoride mouthrinse (W2194-471) containing 0.02% NaF (100 ppm fluoride ion) at pH = 4.2 and the fixed ratio of four essential oils found in Listerine® Antiseptic mouthrinse. The dosing regimen for the test product will be a 20 ml rinse for 30 seconds, twice daily, consistent with current Listerine® Antiseptic mouthrinse label directions. **The negative control** will be FreshBurst Listerine® Antiseptic mouthrinse (W2194-396), a commercially available non-fluoride mouthrinse. The dosing regimen for the negative control will be 20 ml for 30 seconds, twice daily, consistent with its label directions. **The positive control** will be a neutral sodium fluoride mouthrinse (W2194-473) formulated in accordance with FDA anticaries monograph requirements; the mouthrinse will contain 0.02% NaF (100 ppm fluoride ion), and will be used with a dosing regimen of twice daily rinsing with 10 ml for 60 seconds (21 CFR §355.50(d)(2)(ii)).

After a medical/dental history and informed consent are obtained, forty-two qualifying subjects will start a two to three day "lead-in" period for their first randomly assigned treatment leg. During this period, each subject will wear a specially designed partial denture and will use the assigned mouthrinse and dosing regimen without supervision. At the conclusion of this "lead-in" period, two partially demineralized enamel specimens will be mounted on the buccal area of each subject's partial denture. Subjects will continue to use their assigned mouthrinse and dosing regimen for a two-week treatment period. During the treatment period, rinsing will be supervised in the morning on weekdays, and unsupervised in the evening and on weekends and holidays. At the end of the first treatment period, the specimens will be removed for analysis, and the subjects will then start a 4-5 day washout period prior to their second treatment. These procedures will be repeated until each subject has completed all three treatments.

After the specimens are removed from the partial dentures, the samples will be assessed for mineral content change using surface microhardness testing. The specimens will then be analyzed for fluoride uptake using a microdrill biopsy and microdiffusion analysis.

3 ETHICAL AND LEGAL CONSIDERATIONS[a]

It is the responsibility of the investigator that this study be conducted in accordance with the Declaration of Helsinki and according to the guidelines in the attached appendices and in compliance with all applicable laws and regulations of the locale and country where the study is conducted.

It is the responsibility of the investigator that this study not be initiated until the protocol and a copy of the informed consent document have been reviewed and approved by a duly constituted institutional review board (IRB) or ethics committee (EC), and that all local institutional requirements are satisfied. Current regulations are summarized in Appendix C.

It is the responsibility of the investigator to ensure that each subject and/or his or her legal guardian (or caregiver) reads, understands, and signs a document of informed consent prior to the subject's entrance into the study.

It is the responsibility of the investigator to inform the subject that personal information may be examined during audit or monitoring by properly authorized persons but that such information will be treated as strictly confidential and not be made publicly available.

Indemnification of the investigator, coworkers, and the institution is provided as specified in the Clinical Study Agreement. It is the responsibility of the investigator to retain the subject log and subject records as detailed in Appendix C.

4 STUDY DESIGN

4.1 Study Design

This observer-blind, randomized, controlled study will utilize a crossover design. There will be three cells including test product, negative control and positive control. To avoid bias, all analyses will be conducted blindly without knowledge of specimen treatment. The subjects will not be completely blinded due to the difference on dosing regimen.

4.2 Model

All subjects will wear a partial denture bearing two enamel blocks at the buccal flange area. These enamel blocks will have been partially demineralized *in vitro* to create an artificial subsurface lesion ("white spot") before they are mounted on the partial denture. Anticaries efficacy will be assessed using surface microhardness and fluoride uptake.

4.3 Washout Period

At the start of the lead in period, subjects will receive a professional dental cleaning using a fluoride-free prophylaxis paste. There will be a four to five days washout period between the end of a given treatment period and the start of the next lead-in period during which subjects will resume their normal oral hygiene practices with fluoridated toothpaste.

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[a] Appendices C; Other Administrative and Regulatory Procedures (Section 1.1.2, IRB/EC Review and Approval of Study; 1.1.3, Subject Informed Consent; 1.6; Confidentiality of Subject Information; and 2.1, Information Required by Consumer Healthcare Research and Development for Regulatory Review) and D; The Declaration of Helsinki.

4.4 Lead-in Period

There will be a two to three days "lead-in" period before the beginning of each treatment period during which the subjects will use the test rinse for the immediately ensuing leg as directed, but without supervision or enamel specimens in position.

4.5 Treatment Period

There will be a total of three two-week treatment periods. Treatment rinsing will be supervised in the morning on weekdays, and unsupervised in the evening and on weekends and holidays.

5 STUDY POPULATION

5.1 Source and Number of Subjects

Forty-two qualified adult volunteers will be recruited to participate in the study with the intention that thirty-six subjects will complete the entire three legs of the crossover study. All subjects will be from the Indianapolis area and will have been fitted with mandibular functional removable partial dentures specially constructed to contain two enamel specimens on the buccal flange.

5.2 Subject-Selection Criteria

5.2.1 Inclusion Criteria

To be eligible for study participation, subjects must meet the following inclusion criteria:

- males or females, 18 years or older with good general health with no evidence of communicable diseases;
- providing written informed consent and medical history information prior to their participation;
- currently living in a community with a fluoridated water supply (1 ppm F) and not taking fluoride supplements;
- wearing a removable mandibular partial denture with sufficient room in the posterior buccal flange area to accommodate two enamel specimens (required dimensions 10 x 6 mm);
- having good oral health; and
- willing to comply with all subjects' responsibilities as stated in the protocol (e.g. use of only test products during the study, be willing and capable of wearing their removable partial dentures 24 hours per day during the experimental periods, attendance at appointments, etc.).

5.2.2 Exclusion Criteria

Any of the following conditions will exclude subjects from eligibility for study participation:

- A history of significant adverse effects following use of oral hygiene products such as dentifrices and mouthrinses
- A condition requiring the use of antibiotics.
- An inability to comply with study procedures.

5.2.3 Continuance Criteria:

Each subject must meet the following criteria at each visit in order to continue in the study. Subjects may be dropped from the study and/or excluded from the efficacy analyses if there is evidence of:

- Use of non-study mouthrinse during the study;
- Non-compliance with the use of study mouthrinse;
- Development of any of the other exclusion criteria (above).

5.3 Removal of Subjects From the Study

Subjects may withdraw from the study at any time for any reason. The Investigator may also remove subjects from the study at any time for reasons of safety or protocol non-compliance and will document the reason for withdrawal for any discontinued subjects. Subjects withdrawn for medical reasons will be referred to a physician or dentist and will have their condition monitored to resolution or until deemed clinically non-significant. All subjects who discontinue participation before completion of the study will be encouraged to return for an exit oral soft tissue examination. Subjects removed from the study will not be replaced.

5.4 Study Completion[b]

The study will be terminated upon completion of all treatment periods and data analyses.

6 STUDY METHODOLOGY

6.1 Clinical Procedures

Visit 1: Screening and Lead-in for Treatment 1 – Subjects who have been recruited for the study will visit the Institute two to three days prior to the start of the first treatment period. At this time, they will complete an informed consent statement and a medical history form. Upon review of these documents, and assessment of inclusion/exclusion criteria, each potential panelist will be given an oral soft tissue (OST) exam prior to their acceptance into the study. Qualifying panelists will be accepted into the study and will be given a three-week supply of their first test mouthrinse and a non-fluoride toothpaste to use during the first lead-in and treatment period. They will also receive a professional dental cleaning using non-fluoride pumice and will be given detailed instructions on brushing and rinsing procedures and use of their partial denture.

Visit 2: Beginning of Treatment 1 –Two gauze-covered enamel blocks will be mounted in the buccal acrylic flange area of the subjects' mandibular partial dentures (see Fig. 1).

[b] Appendix C; Other Administrative and Regulatory Procedures (Section 3.3. Study Termination)

The subjects will be instructed to wear their partial dentures containing the test enamel blocks at all times (24 hours per day) except during the cleaning of their natural teeth (twice daily) and for short periods to rinse their mouth out with tap water after meals and snacks. Panelists will be given instructions for keeping a product usage diary throughout the treatment period. Panelists will be questioned about their normal dietary habits and encouraged not to change their dietary habits during the treatment periods.

Visit 3: End Treatment 1, Begin Washout for Treatment 2 - At the end of the two-week test period, the two enamel specimens will be recovered from the subjects' partial dentures and evaluated for changes in surface microhardness and fluoride uptake (see Laboratory Procedures). The subjects will receive an oral soft tissue examination. Subjects will be queried regarding any changes to their normal dietary habits that may have occurred over the previous treatment period. Subjects will be encouraged to maintain their normal diet throughout all treatment periods. Subjects will be instructed to use their regular fluoridated toothpaste and brushing regimen during the washout period. They will be encouraged to remove their partial dentures at night during the washout period.

Visit 4: Begin Lead-in for Treatment 2 – After four to five days of washout, subjects will receive a prophylaxis with non-fluoride pumice and will be given their second test mouthrinse and non-fluoride toothpaste to use for next treatment period. They will start their two to three day lead-in period for the second treatment. The subjects will be encouraged to remove their partial denture at night during this lead-in period.

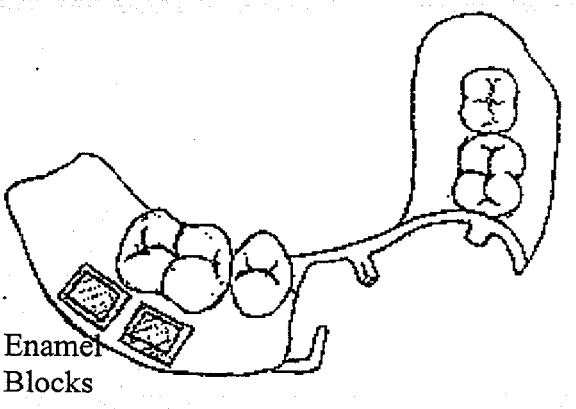
Visit 5: Begin Treatment 2 -After a two to three days of lead-in period, the subjects will repeat the steps outlined for Visit 2 for their second treatment period.

These visits will be repeated until the each subject has completed all three-test regimens. There will be a total of nine visits. The timetable for the study is summarized in Appendix A.

6.2 Intraoral Appliance

This *in situ* model (Zero, 1995) involves the placement of two human enamel blocks in the buccal flange area of each subject's mandibular partial denture (see Figure 1). The subject's denture will be prepared for the study by creating two hollows in the buccal flange area large enough to accommodate the two enamel blocks. The partially demineralized enamel blocks will be mounted on the partial denture and covered with Dacron gauze (cat no. 0001628, USCI, Billerica, MA) to encourage plaque formation (Koulourides et al., 1974; Featherstone and Zero, 1992). The enamel blocks will be mounted in such a manner that the enamel surface of the block is flush with the surface of the buccal flange of the denture. The gauze-covered enamel blocks will be luted in place using a light-cured dental composite (Triad VLC material, Dentsply Int., York, PA). Great care will be taken to avoid contaminating the enamel surface of the blocks with the luting material. During the washout and lead-in periods between test legs, the hollow will be temporarily filled with sticky wax. Upon completion of the study, the partial dentures will be permanently repaired with acrylic. Since the sites at which the enamel blocks are placed are not within a functional part of the denture, the experimental procedures should not cause any permanent damage to the denture.

FIGURE 1. Lower Partial Denture Appliance



6.3 Laboratory Procedures of Specimen Preparation

6.3.1 Disinfection and Preparation of Enamel Blocks

Specimens obtained from human permanent teeth will be used as the hard tissue test substrate in this *in situ* caries model. The teeth will be collected from dental offices. Teeth will be selected based on the following criteria:

- Be free of caries and major restorations.
- Have no discoloration and no markings, such as cracks, when viewed under a dissecting microscope at 15x magnification.
- Sufficient tooth surface to provide a large size specimen to meet study requirements.

The teeth will be transported to the study site in 0.2% thymol. Upon receipt at the Institute, the teeth will be sorted and cleaned and the root tips will be removed. The teeth specimens will then be stored in thymol during sample preparation procedures.

Up to two specimens will be obtained from the buccal and/or lingual smooth surface of each tooth. Longitudinal sections approximately 3mm in thickness will be made parallel to the selected tooth surfaces. The tooth sections will then be cut into 4x4 mm blocks using a Buehler Isomet low-speed saw.

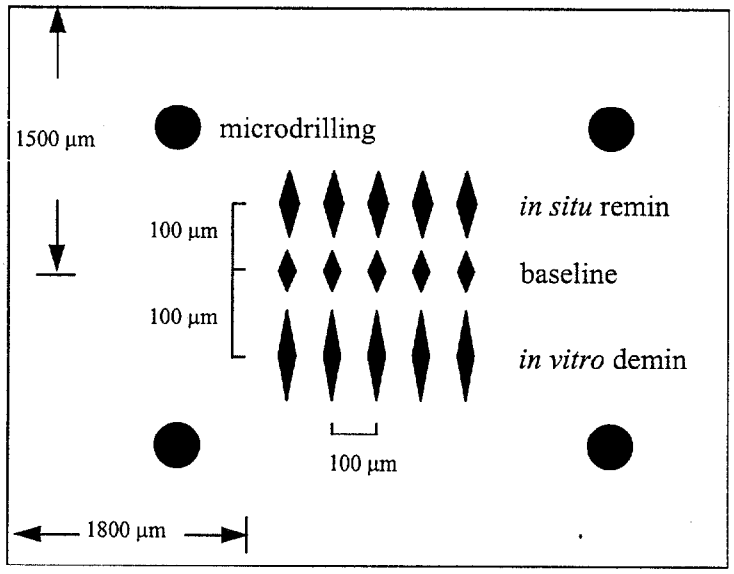
Each block will be ground and polished to create flat surfaces to facilitate surface microhardness (SMH) testing (Zero et al., 1990). Specimens will be ground and polished to create planar parallel dentine and enamel surfaces. The dentine side will be ground flat using 320 grit silicon carbide paper, followed by grinding and polishing of the enamel side. The enamel surface of each block will be ground using 600 grit silicon carbide paper followed by polishing with 1200 grit silicon carbide paper. All grinding/polishing will be done under a steady stream of deionized water. After each grinding/polishing procedure the enamel blocks will be sonicated in double deionized water (ddw) for two minutes and then placed under running ddw for three minutes. The final polishing step will involve the use of a 1 μm diamond abrasive spray on a polishing cloth. The enamel blocks will then be rinsed under a steady stream of ddw, sonicated for two minutes in 2% microliquid soap and then rinsed again with ddw for three minutes.

Before insertion into the subjects' partial dentures, all enamel blocks will be sterilized by exposure to gamma radiation.

6.4 Assessment of Enamel Mineral Content by Microhardness

The surface microhardness (SMH) test will be used to assess changes in the mineral status of sound and partially demineralized enamel blocks. SMH will be measured using a Leitz Miniload Hardness Tester. Each enamel block will be secured on a 1-in. square plastic block with sticky wax and then mounted on the microhardness tester. Five baseline indentations spaced 100 μm apart will be placed with a Knoop diamond under a 50-g load in the center of a flattened, polished sound enamel block. The SMH will be determined by measuring the length of the indentations (μm) using an image analysis system (Costar CVM 2/3 inch CCD 640 x 480 pixel resolution monochrome video camera interfaced with the Leitz Miniload Hardness Tester, Pentium 166 computer, Optimas Imaging System software, Version 6.1).

FIGURE 2. Enamel Block (4x4 mm) for *in situ* Model



6.4.1 The First Microhardness Measurement: at The Baseline

The baseline surface microhardness (SMH) of the enamel blocks (Figure 2) will be determined by placing 5 indentations (B1-B5, B1 = left to B5 = right in Figure 2). For enamel blocks to be acceptable for use in the study, baseline indentation lengths must be 43 ± 3 μm.

6.4.2 The Second Microhardness Measurement: After *in vitro* Demineralization

After the baseline SMH of the enamel blocks is determined, the enamel blocks will be partially demineralized using a modification of the method describe by White (1987) before they are mounted on subjects' partial dentures.

The enamel blocks will be immersed for 24 hours at 37° C in 40 mL of an acid buffer (0.05 mol/L lactate) 50% saturated with respect to hydroxyapatite and with 0.2% (wt/vol) carbopol (Grade 907) added (pH adjusted to 5.0), and then rinsed thoroughly with double

deionized water. The enamel blocks will be stored in a moist environment to prevent dehydration.

After *in vitro* demineralization (described above) the enamel blocks will be again SMH-tested by placing 5 indentations 100 μm directly below the baseline indentations (d1-d5, d1 = left to d5 = right in Figure 2). Only enamel blocks with indentation lengths of 130 ± 20 μm after *in vitro* demineralization will be used in the *in situ* study.

6.4.3 The Third Microhardness Measurement: After Two-week Intraoral Exposure

After 14 days of intraoral exposure the enamel blocks will be removed from the partial dentures. All specimens will be wiped clean with a wet cotton applicator and stored in thymol. The enamel blocks will be again SMH-tested by placing 5 indentations 100 μm directly above the baseline indentations (R1-R5, R1 = left to R5 = right in Figure 2)

6.4.4 Calculation of Percent Surface Microhardness Recovery (% SMH Recovery)

Based on the method of Gelhard et al. (1979), the extent of remineralization for each enamel block will be calculated by:

$$\% \text{ SMH recovery} = \frac{d_i - R_i}{d_i - B_i} \times \frac{100}{1} \qquad \text{for } i = 1 \text{ to } 5$$

B_i = indentation length (μm) of sound enamel block at baseline

d_i = indentation length (μm) after in vitro demineralization

R_i = indentation length (μm) after intra-oral exposure.

where B_i, d_i, and R_i are defined in Sections 6.4.1-6.4.3. The mean %SMH recovery will be calculated within each enamel block, and the mean %SMH recovery will then be computed over the two enamel blocks within a subject. If a subject is missing an enamel block, the mean will be computed over the available enamel block. The mean for each subject will be analyzed as the primary efficacy parameter

6.5 Enamel Fluoride Uptake Using Microdiffusion Method

After surface microhardness analysis as described above, the enamel specimen will be disinfected in 20% ethyl-alcohol for 10 minutes and will be analyzed for fluoride uptake using microdiffusion method after microdrill biopsy. Specimens will be remounted with superglue on plastic rods for support. The drilling and sample collection will be performed in a humidity-controlled atmosphere to prevent loss of enamel powder due to charging effects.

6.5.1 Fluoride Sampling and Analysis

a. The fluoride electrode will be calibrated daily, and calibration data will be recorded.

b. A blank solution (20 μL 0.5 mol/L $HClO_4$ + 40 μL deionized water + 40 μL citrate/EDTA buffer) will be analyzed and the millivolt reading will be recorded. The millivolt reading must be greater than the previous reading for the 0.02 ppm F standard (e.g., if the mv reading for 0.02 ppm F is 142.4, the reading for the blank must be ≥ 144.5).

c. Each sample will be drilled to approximately 100 μm with a reduced size 0.010 x 1/8 SK 2FL SE carbide dental bur.

d. The enamel powder biopsy will be transferred to a polypropylene vial cap which will serve as a microdish for fluoride analysis. The enamel powder will be dissolved in 20 μL 0.5 mol/L $HClO_4$, and 40 μL of deionized water and 40 μL of citrate/EDTA buffer, pH = 8.0, will be added. Each sample will be analyzed immediately after drilling.

e. The fluoride concentration of each sample will be determined from a standard curve constructed at the same time from analyses of the following standard solutions: Deionized H_2O; solutions containing 0.02, 0.04, 0.1, 0.2, 0.4, 1.0, and 4.0 ppm fluoride.

f. After each four (4) enamel fluoride measurements, readings for the 0.04 ppm fluoride standard and blank will be repeated (as described above), and these data will be recorded.

6.5.2 Calculation of Enamel Fluoride Uptake

Data from each fluoride analysis will include: the drill hole depth; the drill hole diameter; fluoride electrode reading in millivolts; fluoride concentration in μg/mL (ppm); and calculated fluoride uptake in $\mu g/cm^2$. The amount of fluoride-uptake by enamel will be calculated based on the amount of fluoride (F) divided by the area of the enamel cores and expressed as $\mu g\ F/cm^2$.

6.6 Efficacy Assessments

6.6.1 Primary Efficacy Parameter

The primary efficacy parameter will be percent surface microhardness recovery (see section 6.4). The mean for each subject will be analyzed as the primary efficacy parameter.

6.6.2 Secondary Efficacy Parameter

The secondary efficacy parameter will be the amount of enamel fluoride uptake, calculated based on the amount of fluoride divided by the area of the enamel cores and expressed as $\mu g\ F/cm^2$.

6.7 Safety Assessments[c]

Each subject will receive an oral soft tissue (OST) exam prior to and following each treatment leg. The OST will be performed as described in Appendix E. All subjects will be questioned at the beginning and end of each treatment period regarding any general health or oral complaints they have experienced since entering into the study. Any complaints and/or adverse effects (AE) will be documented on the adverse effects clinical record form described in Appendix B.

6.7.1 Adverse Event Reporting[d]

Any new or continuing sign or symptoms will be observed and recorded for each subject at each visit during the study as detailed in Appendix B.

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[c] Appendix E; Study Safety Procedures
[d] Appendix B; Administrative Procedures for Reporting Adverse Events

6.7.2 Serious Adverse Events

Report immediately to Consumer Healthcare Research and Development any serious adverse event defined as any adverse event at any dose that results in any of the following outcomes:

- Death;
- Life-threatening adverse event;
- In-patient hospitalization or prolongation of existing hospitalization;
- Persistent or significant disability/incapacity;
- Congenital anomaly/birth defect; or
- Clinically significant medical events judged by principal investigator (includes clinical laboratory abnormalities)

IN CASE OF SERIOUS OR LIFE-THREATENING ADVERSE EVENTS, OR IN THE EVENT OF DEATH, A CONSUMER HEALTHCARE RESEARCH AND DEVELOPMENT COLLEAGUE MUST BE CONTACTED IMMEDIATELY.[e]

Jane Zhang
Warner-Lambert Company
170 Tabor Road
Morris Plains, NJ
Phone: (973-385-3345)

If any serious adverse event occurs, interrupt or discontinue study treatment at your (the dentist investigator) discretion. If in an acute medical emergency the Consumer Healthcare Research and Development colleague cannot be contacted, you may break the randomization code only if this is required for proper treatment of the subject.[f] Notify the Consumer Healthcare Research and Development colleague of emergency code breaks as soon as possible.

6.7.3 Lack of Efficacy

Lack of efficacy should not be captured as an adverse event.

6.7.4 Adverse Event Follow-up

In following up adverse events, attempts should be made to obtain as much information as possible about event evolution and outcome.

7 STUDY TREATMENT[g]

7.1 Test Materials

[e] Appendix B; Administrative Procedures fore Reporting of Adverse Events (Section 4.1, Immediately Reportable Adverse Events)
[f] Appendix C; Other Administrative and Regulatory Procedures (Section 1.6, Emergency Information)
[g] Appendix C; Other Administrative and Regulatory Procedures (Section 1.5. Medical Intervention and Code Breaking; Section 2.5. Investigator's Responsibility for Clinical Product Supply Accountability)

Table 1. Test Materials and Dosing regimens

FUNCTION OF THE CELL	PRODUCT NAME AND BRIEF DESCRIPTION	DOSING REGIMENS	PRODUCT NUMBER
Test product	FreshBurst Listerine® mouthrinse with 0.02% sodium fluoride, (F^- =100 ppm)	20 ml for 30 seconds, twice daily	W2194-471
Positive control	Neutral 0.02% NaF mouthrinse (F^-=100 ppm), compliant with FDA monograph	10 ml for 60 seconds, twice daily	W2194-473
Negative control	FreshBurst Listerine® Mouthrinse	20 ml for 30 seconds, twice daily	W2194-396

All test mouthrinses will be produced by Warner-Lambert Company using Good Manufacturing Practices.

7.2 Other Study Material

Fresh'n Brite® Denture Toothpaste (W9979-18), a non-fluoride toothpaste, will be used from the beginning of the lead-in period to the completion of each treatment period in order to reduce background fluoride level. This denture toothpaste has been proven to be safe for intraoral use.

7.3 Labeling

A label will be affixed to the mouthrinse supplies. All bottles will be labeled with a clinical test label containing the study number, subject number, a code letter that is assigned by the Sponsor for identifying the contents of the bottles, and a dosing regimen and caution statement. The Sponsor will provide a master list of the code identification to the study coordinator in sealed envelopes that will be kept in the coordinator's study file. The envelopes will be opened only if it becomes necessary, such as in the case of an adverse response, to identify the product given to a particular subject.

7.4 Shipment and Storage

The study clinical supplies (W2194-396, W2194-471 and W2194-473) will be shipped to the investigator from Warner-Lambert Company. The contents of the shipment should be verified with the shipping invoice. All study test supplies should be stored in a secure, locked area at room temperature, and be available for accountability during scheduled visits by the study monitor.

7.5 Maintenance of Product Dispensing Records

The mouthrinse dispensing record should be kept current during the study and be available for inspection by the Warner-Lambert monitor.

7.6 Assignment of Subjects to Product Use

All subjects will be identified by a unique study number. Subjects will be randomly assigned to use one of the treatment regimens in the order of entry into the study. Randomization will be determined from a standard randomization table provided by the sponsor for the number of products in the crossover study.

7.7 Product Use

7.7.1 Lead-in Period

Two to three days before the first treatment period, the subjects will be given their first test mouthrinse and a non-fluoride toothpaste to use. Subjects will wear their partial denture during the day and be encouraged to remove their partial denture during the night. Subjects will brush their teeth twice daily with non-fluoride toothpaste and rinse with their assigned mouthrinse according to the appropriate regimen. All rinses will be unsupervised. Subjects will be instructed not to eat or drink for 30 minutes after rinsing.

7.7.2 Test Period

At the start of each treatment period, two enamel specimens will be mounted on the buccal side of each partial denture. Subjects will continue to use the non-fluoride toothpaste and their first randomly assigned test mouthrinse. Subjects will wear their partial dentures 24 hours a day during each treatment period, except when brushing their nature teeth or while rinsing their partial denture with water after eating. To brush their teeth, subjects will first remove their partial denture and brush their natural teeth with the non-fluoride dentifrice and rinse with water. They will then brush their partial denture with their non-fluoride toothpaste and rinse with water, taking care not to brush the specimen sites. The subjects will then return their partial denture to their mouth. They will rinse their mouth with their assigned mouthrinse and dosing regimen. The morning rinse of each treatment period will be supervised on weekdays at the study site; evening rinses and those on weekends and holidays will be unsupervised. Subjects will be instructed to use their rinse right after toothbrushing, except for the supervised rinse. They will be instructed not to eat or drink for 30 minutes after rinsing. Subjects will be instructed to use no other dental care products (e.g. dentifrices, rinses, gels, whiteners etc) during the study period. Subjects may continue to floss their teeth if they routinely flossed prior to initiating the study.

7.8 Return of Study Product

After the study completion, all subjects will return all mouthrinse and toothpaste containers to the clinic and the containers will be sent to:

CCPO
Warner-Lambert Company
175 Tabor Road
Morris Plains, NJ 07950

7.9 Subject Compliance

Subjects will be required to return all product containers (even empty ones) to the clinical coordinator at the completion of each treatment period. Subjects' compliance will be monitored by determining the amount of product used. For the supervised rinses, subjects must complete at least 8 supervised rinses for each test leg, with no more than two consecutive rinses missing. For the unsupervised rinses, subject compliance will be checked by weighing the product containers before and after each leg. The difference between actual weight used and expected weight should be within 20% of the expected weight. Product usage diaries in which subjects will be asked to record the time of daily product usage will also be used to monitor subject compliance.

8 DATA COLLECTION

Case Report Forms for Consumer Healthcare Research and Development will be supplied for all subjects. These are to be completed as instructed. Original CRFs and other study documentation, as determined, will be returned to Warner Lambert. Consumer Healthcare Research and Development will perform monitoring.

9 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

9.1 Data Analysis [h]

Data management and statistical analyses will be performed by the Statistics and Data Management Department of the Warner-Lambert Consumer Healthcare Research & Development Division.

9.2 Primary Efficacy Parameter

The primary efficacy parameter will be % recovery of surface mineral hardness (%SMH recovery, Zero, 1995) calculated using the equation:

$$\% \text{ SMH recovery} = \frac{d_i - R_i}{d_i - B_i} \times \frac{100}{1} \qquad \text{for } i = 1 \text{ to } 5$$

B_i = indentation length (μm) of sound enamel block at baseline

d_i = indentation length (μm) after in vitro demineralization

R_i = indentation length (μm) after intra-oral exposure.

where B_i, d_i, and R_i are defined in Sections 6.4.1-6.4.3.. The mean %SMH recovery will be calculated within each enamel block, and the mean %SMH recovery will then be computed over the two enamel blocks within a subject. If a subject is missing an enamel block, the mean will be computed over the available enamel block. The mean for each subject will be analyzed as the primary efficacy parameter

9.3 Secondary Efficacy Parameter

The secondary efficacy parameter will be the amount of fluoride-uptake by enamel and will be calculated based on the amount of fluoride divided by the area of the enamel cores and expressed as μg F/cm^2.

9.4 Data Sets Analyzed

The primary efficacy analyses will be based on evaluable subjects, defined as all randomized subjects with no major protocol violations who have evaluable data for each treatment period. Efficacy analyses will also be performed using all randomized subjects. Demographic analysis will also be performed both for evaluable subjects and for randomized subjects.

9.5 Demographic Variables

Age, race, and gender will be summarized by treatment sequence and over all treatment sequences.

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[h] Appendix C; Other Administrative and Regulatory Procedures (Section 1.7. Publication or Presentation of Results)

9.6 Efficacy Analysis

The primary research question is:

- Is the test fluoride mouthrinse (W2194-471) effective in providing enamel remineralization?

The secondary research questions are:

- Is the test fluoride mouthrinse (W2194-471) effective in increasing enamel fluoride?
- Is the study validated?

To address these questions, between-treatment comparisons will be performed using a mixed model with sequence, treatment, period, and carryover as fixed, and with subject as random.

The following comparisons will be made for each efficacy parameter. For each comparison, the null hypothesis is that the treatment means are equal, and the alternative hypothesis is that the treatment means are different.

- Test fluoride mouthrinse (W2194-471) vs. negative control rinse (W2194-396).
- Positive control (W2194-473) vs. negative control (W2194-396).

The study will be considered validated if the mean %SMH recovery for the positive control is statistically significantly higher than the mean %SMH recovery for the negative control.

Each comparison will be performed at the 0.05 level, two-sided. As the first comparison is of primary interest, and the second comparison is for study validation, no multiple comparisons adjustment will be performed.

The test product (W2194-471) will be considered to be effective if it is statistically significantly more effective in promoting recovery of surface microhardness than the negative control rinse, and the study is validated (i.e. the positive control is significantly more effective than the negative control).

For additional information, the test product (W2194-471) will be statistically compared with the positive control at the 0.05 level, two-sided, with respect to each efficacy parameter. The null hypothesis for this test is that the treatment means are not different, and the alternative hypothesis is that the treatment means are different.

9.7 Statistical Power and Sample Size Considerations

The planned sample size of 36 completed, evaluable subjects will provide 90% power to detect a between-treatment difference in %SMH recovery of 15, based on a two-sided 0.05-level test and a standard deviation of 19. The standard deviation estimate of 19 was derived from previous microhardness studies conducted by the investigator.

9.8 Interim Analysis

No interim analyses will be performed.

10 REFERENCES

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6. Zero DT, Fu J, Espeland MA, Featherstone JDB (1988) Comparison of fluoride concentrations in unstimulated whole saliva following use of a fluoride dentifrice and a fluoride rinse. J Dent Res 7:1257-1262.

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8. Zero DT (1995) *In situ* Caries Models. Advances in Dental Research 9:214-230.

11 APPENDICES

A. Timetable of Visits and Procedures
B. Administrative Procedures for the Reporting of Adverse Events
C. Other Administrative and Regulatory Procedures
D. Declaration of Helsinki
E. Study Safety Procedures
F. Case Report Forms

APPENDIX A

TIMETABLE OF VISITS AND PROCEDURES

VISIT	DATE	NAME OF THE VISIT	PROCEDURES AT CLINIC	PRODUCT DISTRIBUTION
1	Day 1	Subject Enrollment Leg 1, Lead-in	Screening, dental cleaning OST* Exam	Non–fluoride Toothpaste, Toothbrush, Leg 1 Mouthrinse
2	2-3 days after visit 1	Leg 1, Treatment	Specimen Placement	
3	14 days after visit 2	Finish Leg 1, Leg 2, Washout	Specimen Removal OST Exam	
4	4-5 days after visit 3	Leg 2, Lead-in	Dental cleaning	Non –fluoride Toothpaste, Toothbrush, Leg 2 Mouthrinse
5	2-3 days after visit 4	Leg 2, Treatment	Specimen Placement	
6	14 after visit 5	Finish Leg 2, Leg 3, Washout	Specimen Removal. OST Exam	
7	4-5 days after visit 6	Leg 3, Lead-in	Dental cleaning	Non–fluoride Toothpaste, Toothbrush, Leg 3 Mouthrinse
8	2-3 days after visit 7	Leg 3, Treatment	Specimen Placement	
9	14 days after visit 8	Finish Leg 3	Specimen Removal Exit OST exam	

*OST Exam: Oral Soft Tissue Exam

APPENDIX B
Administrative Procedures for Reporting of Adverse Events

APPENDIX B

Administrative Procedures for the Reporting of Adverse Events

INTRODUCTION

The administrative procedures for reporting adverse events described in this appendix are to be followed during the conduct of this protocol.

If you have any questions concerning adverse event reporting, please contact the Consumer Healthcare Research and Development colleague or representative who is monitoring your site or a Consumer Healthcare Research and Development colleague whose name, address, and telephone number appears on the cover sheet to this protocol.

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1. ADVERSE EVENTS DURING THE STUDY

Each subject will be observed and queried in a nonspecific fashion by the investigator or study coordinator at each visit during baseline, study treatment, and protocol-defined follow-up for any new or continuing adverse events (AEs) since the previous visit. Any new AEs or ones changing in character, frequency, or in intensity reported by the subject or caregiver or noted by the investigator or study coordinator after the signing of the informed consent will be recorded on the AE Case Report Form (CRF).

The investigator will review any clinical laboratory test results in a timely fashion when received from the laboratory. Those results qualifying as AEs as defined in Sections 2 of Appendix B. This appendix will be recorded on the AE CRF and will be handled according to these administrative procedures for reporting AEs.

The investigator will review concomitant medications being taken by the subject. The AE that led to the administration of any new concomitant medications (not specified in the protocol) will be reported on the AE CRF.

2. DEFINITIONS

Pre-Existing Conditions

A pre-existing condition is one that is present at the start of study treatment.

Baseline

Defined by the Therapeutic Group for each program.

Adverse Event

Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Related Adverse Event

An AE where there is a reasonable possibility that the event may have been caused by drug (Unknown is also considered related).

Serious Adverse Event (SAE)

Any adverse event occurring at any dose that results in any of the following outcomes:

- Death;
- Life-threatening adverse event;
- In-patient hospitalization or prolongation of existing hospitalization;
- Persistent or significant disability/incapacity;
- Congenital anomaly/birth defect; and
- Medically significant event (includes laboratory abnormalities).

Medically significant events may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse, or laboratory abnormalities.

The following hospitalizations are not considered SAEs:

- For diagnostic or elective surgical procedures for a pre-existing condition;
- For therapy of the target disease(s) of the study if the protocol explicitly anticipated and defined the symptoms or episodes;
- For study efficacy measurement, as defined in the protocol.

Life-Threatening Adverse Event

Any adverse event that places the subject or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Unexpected Adverse Event

Any adverse event, the specificity or severity of which is not consistent with the current Investigator's Brochure. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator's Brochure only referred to elevated hepatic enzymes or hepatitis.

Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator's Brochure only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an AE that has not been previously observed (e.g., included in the Investigator's Brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the product.

Clinical Laboratory Adverse Event

A clinical laboratory abnormality that is regarded as an AE if it has been confirmed by at least 1 repeat test and suggests a disease and/or organ toxicity of a severity that requires active management, e.g., change of dose, discontinuation of drug, more frequent follow-up, diagnostic investigation, etc.

Treatment-Emergent Signs and Symptoms (TESS)

Any AE that was not evident during baseline as defined by the study protocol or that increases in intensity or frequency, or changes in character during treatment.

Post-Treatment Adverse Event

Any AE that occurs after study treatment is discontinued. Post-treatment follow-up and post-treatment adverse events of interest to the study will be defined per protocol.

Lack of Efficacy

A worsening of the disease being studied or lack of desired effect of the study drug (not reported as an AE if defined as an efficacy parameter in the protocol).

2.1. Attributes of Adverse Events

2.1.1. Treatment-Emergent Signs and Symptoms (TESS)

Any condition/diagnosis that meets the definition of a TESS event is captured as such on the AE CRF.

2.1.2. Serious Adverse Events

All SAEs, as defined in Section 2, are immediately reportable to the Sponsor within 24 hours of the Investigator's first knowledge of the event (see Section 4.1 of this appendix).

If there is an exception to the SAE definition, it is described in the protocol.

2.1.3. Intensity

The following criteria are used to assess the intensity of each AE:

Mild: The subject is aware of the sign or symptom, but finds it easily tolerated.

Moderate: The subject has discomfort enough to cause interference with or change usual activities.

Severe: The subject is incapacitated and unable to work or participate in many or all usual activities.

Not Applicable:

Note: For oncology studies, in lieu of these criteria, standardized coding criteria may be used as defined in the protocol.

2.1.4. Relationship to Study Drug—Physician's Assessment

Causality will be captured by the investigator on the CRF Adverse Events as one of the following choices:

(a) Probable
A clinical event, including a laboratory test abnormality, which meets **all** of the following criteria:

i. Occurs within a reasonable time sequence to administration of the drug.
ii. Is unlikely to be attributed to concurrent disease or other drugs or chemicals.
iii. There is a positive dechallenge; that is, the event follows a clinically reasonable response on withdrawal.
iv. Rechallenge information is not required, or may be unclear or not applicable. However, if the information is available, rechallenge is positive; that is, the event recurs upon reintroduction.

(b) Possible
A clinical event, including a laboratory test abnormality, which meets **all** of the following criteria:

i. Occurs within a reasonable time sequence to administration of the drug.
ii. Could also be explained by the presence of concurrent disease or other drugs or chemicals.
iii. Dechallenge information is not required, or may be unclear or not applicable. However, if the information is available, dechallenge may be positive or negative; that is, the event may or may not follow a clinically reasonable response on withdrawal.
iv. Rechallenge information is not required, or may be unclear or not applicable. However, if the information is available, rechallenge may be positive or negative; that is, the event may or may not recur upon reintroduction.

(c) Unlikely
A clinical event, including a laboratory test abnormality, which meets **one** of the following criteria:

i. The temporal relationship (time sequence to drug administration) makes a causal relationship improbable or
ii. Other drugs, chemicals, underlying disease, or other factors provide more plausible explanations.

2.1.5. Clinical Outcome

The following categories are used to assess the clinical outcome of each AE:

Recovered (with or without residual effects):

The subject has fully recovered from the AE with or without observable residual effects.

Not Yet Recovered:

The subject is still being treated for the residual effects of the original AE. This does not include treatment for pre-existing conditions including the indication for the study drug.

Died Due to This Adverse Event

Died, Other Causes

Unknown

Surgery/Procedure

3. CAPTURING ADVERSE EVENTS

3.1. Pre-Existing Condition

A pre-existing condition should be reported as an AE if the frequency, intensity, or the character of the condition worsens during study treatment.

3.2. Lack of Efficacy

Signs or symptoms defined in the protocol as lack of efficacy or collected as efficacy parameters should not be reported as AEs.

3.3. Clinical Laboratory Adverse Event

A clinical laboratory abnormality should be reported as an AE only if the conditions are met as defined in Section 2.

3.4. Hospitalization or Surgery/Procedure

Any AE that results in hospitalization (i.e., subject admitted—not just an emergency room visit) should be reported as an SAE except as described in Section 2 of Appendix D or unless specifically instructed otherwise in the protocol. Any condition/diagnosis responsible for surgery/procedure should be reported as an AE if it meets the criteria for an AE. The surgery/procedure itself will be reported as a Clinical Outcome of the underlying event.

Events that prolong any hospitalization are reported as SAEs.

3.5. Death

The cause of death should be reported as an AE. Death should not be reported as an AE, but as a Clinical Outcome. The only exception is "Sudden Death" when the cause of death is unknown, which is reported as an AE with death as the Clinical Outcome.

3.6. General Physical Examination Findings

At screening, any clinically significant finding should be recorded on the General Medical History CRF. After the signing of the informed consent document, any new clinically significant finding that meets the definition of an AE must be documented as such.

4. RECORDING AND REPORTING

All AEs that occur at any time during the study including the posttreatment period as defined in the protocol, are to be reported in the subject's CRFs. The investigator should attempt, if possible, to establish a diagnosis based on the presenting signs and symptoms.

If the event meets the definition of a "serious" adverse event, a photocopy or fax of the Warner-Lambert Serious Adverse Event Report, the Adverse Event Case Report Form, and Concomitant Medication Case Report Form, and/or other pertinent information must be provided within 24-hours to the clinical monitors. Warner-Lambert Company will monitor the completeness and accuracy of these forms.

At each visit, after the subject has had an opportunity to spontaneously mention any problems, the investigator should inquire about adverse events by asking the following standard questions:

a. "Have you had any (other) medical problems since your last visit?"

b. "Have you taken any new medications, other than those given to you in this study, since your last visit?"

All unresolved adverse events observed at the last study visit should be followed by the investigator until the events are resolved, stabilized, the subject is lost to follow-up, or the

events are otherwise explained. All follow-up information should be reported to Warner-Lambert Company.

Adverse events will be recorded at each clinic visit. All adverse events should be recorded on the Adverse Events page of the Case Report Form including date of onset and cessation, intensity and relationship to study drug. The action taken and clinical outcome of SERIOUS adverse events must be reported to the Clinical Monitor without delay. All medical problems occurring since the previous visit which were not present at the initial must be recorded. If there is worsening of a medical condition that was present at the initial visit, this should also be reported. This information is obtained by questioning the subject and/or caregiver and/or examining the subject.

4.1. Immediately Reportable Adverse Events

The investigator or designee must report the occurrence of any serious adverse event to the Warner-Lambert Company within 24 hours, regardless of the causal assessment to study medication, and followed up with a detailed written explanation of the event within 3 days.

A photocopy or fax of the Warner-Lambert Serious Adverse Event Report, the Adverse Event Case Report Form, and Concomitant Medication Case Report Form, and/or other pertinent information must be provided within 24-hours to:

Jane Zhang
Oral Care Technology Development
Consumer Healthcare R & D
Warner-Lambert Company
170 Tabor Road
Morris Plains, NJ 07950
Tel: 973-385-3345
Fax: 973-385-4300

The investigator is responsible for continuing to report to Warner-Lambert Company, within 24 hours, any new or relevant follow-up information on the serious adverse event as the information becomes known to the investigator. All unresolved serious adverse events should be followed by the investigator until the event has resolved, stabilized, the subject is lost to follow-up, or the event is otherwise explained.

4.2. Other Adverse Events

AEs that are not immediately reportable according to the definitions in this appendix will only be recorded on the standard AE CRF. These forms will be collected by the sponsor after the event is resolved, or if the event is continuing, at approximately 12- to 16-week intervals until after the AE ends or if the AE does not end, until the subject completes the study or the protocol-specified follow-up period.

4.3. Follow-Up Period

For SAEs, the subject must remain under observation until the SAE has subsided or stabilized and all serious pathological values and findings have returned to normal or stabilized.

Follow-up information will not be collected for "not yet recovered" or continuing nonserious AEs unless time frames are specifically written in the protocol.

APPENDIX C
Other Administrative and Regulatory Procedures

APPENDIX C

Other Administrative and Regulatory Procedures

INTRODUCTION

This appendix provides information necessary to administer this study in compliance with global GCPs, government regulations, and the policy and procedures of Consumer Healthcare Research and Development Pharmaceutical Research, Warner-Lambert Company.

If you have any questions concerning the conduct of the study, contact one of the Consumer Healthcare Research and Development Medical/Dental Colleagues whose name, address, and telephone number appears on the signature sheet to this protocol.

Your signature on this protocol, any subsequent amendments and addenda, and the Clinical Study Agreement confirms that you:

Have been given appropriate information on the study drug;

Have read and understood the protocol and appendices;

Agree to conduct the study in accordance with the provisions of the protocol and applicable regulations;

Acknowledge Consumer Healthcare Research and Development' ownership of the data and results obtained from the conduct of this protocol; and

Agree to maintain the confidentiality of certain information (see Section 1.8.1)

TABLE OF CONTENTS

1. ADMINISTRATIVE PROCEDURES

1.1. Ethics and Informed Consent

1.1.1. Declaration of Helsinki

This study will be conducted in accordance with the Declaration of Helsinki.

1.1.2. Institutional Review Board (IRB) or Ethics Committee (EC) Review and Approval of the Study

An IRB/EC, that is organized and operates according to GCP and applicable laws and regulations, should safeguard the rights, safety, and well being of all trial subjects. No subject should be admitted to a trial before the IRB/EC issues its written approval/favorable opinion of the trial.

The investigator is responsible for:

- Promptly reporting to the IRB/EC all changes in the research activity, and all unanticipated problems involving risks to human subjects or others;
- Not making any changes in the research without IRB/EC approval, except when absolutely necessary to eliminate apparent immediate hazards to human subjects;
- Submitting a progress report describing the status of the clinical investigation to the IRB/EC at appropriate intervals not exceeding 1 year; and
- Submitting a final report when required by the IRB/EC within 3 months following completion, termination, or discontinuation of the study. Copies of these reports will also be provided to Consumer Healthcare Research and Development.

In general, all communications with the IRB/EC regarding the study of a Consumer Healthcare Research and Development drug will be handled by the principal investigator (or coordinating investigator, if applicable) of the study. Consumer Healthcare Research and Development personnel may directly contact the IRB/EC if necessary but must not attempt to influence the IRB/EC in any way. A copy of all communications from the IRB/EC to the investigator regarding its review of and initial approval of the study and its reapprovals at intervals must be provided to the Consumer Healthcare Research and Development Site Monitor/Clinical Research Associate by the investigator.

1.1.3. Subject Informed Consent

The investigator must fully explain the purpose of the study to the subject or his/her guardian prior to entering the subject into the study. The investigator is responsible for obtaining written informed consent from each subject. For subjects under the legal age of consent or unable to provide written consent, written informed consent must be obtained from his/her legal guardian, or legal representative. Also, the assent of a child to participate in the study must be obtained when appropriate, e.g., in consideration of the child's age and maturity.

Consumer Healthcare Research and Development requires that informed consent be obtained orally and on a written form prepared by the investigator and approved by the IRB/EC. Although a sample Informed Consent Document (ICD) may be provided to international investigators or a template to US investigators, the investigator is ultimately responsible for the content of the document.

The person signing the consent form will receive a copy of the signed form. The signed consent form will be filed at the site with the investigator's copies of the Case Report Forms (CRFs) for each subject.

1.2. Clinical Evaluations Not Specified in the Protocol

Procedures not specified in the protocol can be conducted only if required for the successful management of a subject or they will not affect the conduct or results of the study and each procedure should be approved by the Consumer Healthcare Research and Development Medical/Dental Colleague.

1.3. Monitoring the Study

Frequent contact between the principal investigator and Consumer Healthcare Research and Development will be maintained by the Medical/Dental Colleague and/or the Site Monitor/Clinical Research Associate, or comparable persons from a designated Contract Research Organization appointed by Consumer Healthcare Research and Development, to assure that this study is conducted according to the protocol and that all forms are accurate and complete prior to being forwarded to Consumer Healthcare Research and Development.

1.3.1. Pre-study Visit

Representatives from Consumer Healthcare Research and Development, usually those who will monitor the site, will visit the investigator, site staff, and study facility prior to initiation of the clinical study to:

Review the key elements of the available information on the investigational drug and the protocol;

Determine the site's ability to conduct the study based on, for example, experience, adequacy of physical facilities;

Assess availability of an adequate, suitable subject population; and

Assess IRB/EC involvement and accessibility for Site Monitor/Clinical Research Associate visits including source document verification against medical records.

If the prospective investigator has conducted a study for the Company within the last 12 months with the same investigational drug, a telephone interview may be used to replace an on-site visit at the discretion of the Senior Director.

1.3.2. Investigators' Meeting

Principal investigators must not enroll subjects into a study unless they have received training on all aspects of a clinical study. For multicenter studies, this training is typically provided at an Investigators' Meeting. A prestudy Investigators' meeting is a formal meeting between the sponsor and the investigators and their staff to review all aspects of a clinical study prior to study initiation. The main purposes of this meeting is to:

- Review the study protocol and procedures;
- Resolve any questions regarding the purpose(s) and conduct of the study;
- Instruct all participants in the administrative and regulatory (i.e., GCP) procedures to be followed.

For some studies, the Senior Director may waive the Investigator's Meetings if the goals have been accomplished via a Prestudy Visit and/or Investigators' Meeting or the site has participated in other similar studies for Consumer Healthcare Research and Development within the past 12 months.

1.3.3. Study Initiation Visit

This visit, which is conducted by the Site Monitor/Clinical Research Associate, typically occurs after the Investigators' Meeting and after written study materials and clinical supplies are at the site, and before subject enrollment. The purpose of this visit is to ensure that both Consumer Healthcare Research and Development and the investigator have fulfilled all necessary obligations before treating subjects in a clinical trial. During the visit, the Site Monitor/Clinical Research Associate reviews with the investigator and

appropriate site staff the key elements of study documents and supplies and their study obligations and roles.

1.3.4 Monitoring Visits and Phone Contacts

Routine monitoring visits, at appropriate intervals detailed in the monitoring guidelines, will be scheduled based on the design and complexity of the protocol and the timelines for obtaining study results to:

- Verify that the rights and well-being of human subjects are protected (e.g., signed informed consent document, IRB/EC approvals, etc);
- Ensure study conduct in accordance with the protocol (and any amendments), local regulatory requirements, Consumer Healthcare Research and Development procedures, and GCPs;
- Verify the accuracy and timely ensure completion of the recorded data (e.g., CRFs) with respect to source documents (see Section 1.3.4.1 below);
- Resolve data queries;
- Verify that data and biological samples are collected n a timely manner;
- Maintain an accurate record of study progress;
- Account accurately for clinical drug supplies;
- Ensure continued acceptability of facilities for study conduct;
- Ensure appropriate maintenance of required documents;
- Prepare the site for audits.

In addition, both Consumer Healthcare Research and Development and the site are responsible for documenting substantive telephone conversations (e.g., those about inclusion/exclusion criteria in the protocol, medication dosing procedures, adverse events, and emergency code breaks).

1.3.4.1.Source Data Verification

The purpose of Source Data Verification (SDV; also known as Source Document Verification) is to ensure as much as possible the accuracy, quality, and reality of the data recorded on CRFs via a comparison to source documents. Source documents are the original documents or records where raw/source data concerning a subject have been first recorded, e.g., medical charts, hospital records, clinical laboratory reports, X-rays, automated instrument tracings, signed and dated informed consent documents.

1.3.5. End-of-Study Visit

The final on-Site Monitor visit is conducted when:

- The investigator completes the study or requests to discontinue participation in the study; or
- Consumer Healthcare Research and Development decides to discontinue the study for all investigators in a trial (e.g., due to adverse events or study enrollment being reached) or for an individual investigator (e.g., due to poor subject enrollment).

Purposes of the End-of-Study Visit include:

- Reviewing and ensuring completeness of required documentation and documentation retention policies;
- Collecting completed CRFs;
- Ensuring that all adverse events have been identified, documented and reported to Warner Lambert;
- Ensuring final returning/disposition of any remaining clinical drug supplies;
- Ensuring that the investigator has notified the IRB/EC of study completion or discontinuation;
- Reviewing processes that occur after the End-of-Study Visit; and
- Finalizing payment issues.

1.3.6. Communicating Deficiencies

The Consumer Healthcare Research and Development Site Monitor/Clinical Research Associate will inform the site of any deficiencies related to the conduct of the study noted during monitoring visits or audits conducted by Consumer Healthcare Research and Development QA colleagues.

1.4. Randomization Code

The Statistics and Data Management Department of Consumer Healthcare Research and Development or designee generates the randomization code, and then Consumer Healthcare Research and Development or other designated facility will provide product assembled based on a randomization code.

1.5. Medical Intervention and Code Breaking

If any adverse event requires medical intervention, the study medication may be discontinued and the subject treated at the discretion of the physician investigator. In an acute medical emergency, the product assignment code may be broken if this is considered essential for subject management. For this purpose, the product assignment code will be provided to the investigator in a sealed envelope. However, **before breaking the code**, an attempt must be made to contact the Warner-Lambert Monitor. If not possible, contact should be made at the first opportunity. If the code is broken, a record of the time and reason must be put in writing and sent to the Warner-Lambert Monitor. This letter will become part of the permanent study record. The investigator's copy of the sealed product assignment code must be returned to Warner-Lambert at the end of the study.

1.6. Confidentiality of Subject Information

All subjects will be assigned a study subject number. Subsequently, subjects will be identified in the CRFs only by their initials and that number. Any information published as a result of the study will be such that it will not permit identification of any subject. The information from this study will be available within Consumer Healthcare Research and Development and may be shared with the regulatory authorities. It may also be the subject of an audit by a regulatory agency (e.g., FDA) within the local government. The subject's identity will remain protected except as required for legal or regulatory inquiries.

1.7. Publication or Presentation of Results

Upon written permission from Warner-Lambert, the investigator shall be free to publish, present or use any results arising out of the performance of the study for their own instructional, research or publication objectives. Any proposed oral or written use of such results by the investigator shall be submitted to Warner-Lambert for review at least forty-five (45) days prior to submission for publication, presentation or use. This condition is stated so that Warner-Lambert will be aware of all written and oral presentations of the data and does not imply any editorial review or restriction of the contents of the presentation or use.

Warner-Lambert shall reserve the right to deny publication or presentation of the data or to request modification of any publication, presentation or use of study results if such publication, presentation or use will jeopardize a patent application or patent. If the investigator does not consent to such modification, independent patent counsel will be consulted at Warner-Lambert's option; provided that the decision of such patent counsel shall serve only as guidance to, and shall not be binding upon, the investigator.

Further, if there are medical reasons justifying submission for publication, presentation or use sooner than 45 days after submission to Warner-Lambert, Warner-Lambert Company will use its best efforts to expedite review and reduce the 45-day period.

1.7.1. Intellectual Property Rights

By signing a Clinical Study Agreement, the investigator agrees to keep in confidence and use only for completion of the study:

- Information provided to him/her by or on the behalf of Consumer Healthcare Research and Development; and
- Data, inventions, and discoveries, generated as a result of the study.

The investigator also agrees to return all copies of such information to Consumer Healthcare Research and Development at the sponsor's request and that data, inventions, and discoveries generated during the course of this study shall be the property of Consumer Healthcare Research and Development and will sign any documents, if requested, to transfer such ownership. This obligation will not apply to any information or data that later becomes public knowledge.

1.8. Restriction for Subject Inclusion

Study site personnel and immediate family are excluded from enrollment.

2. DOCUMENTATION PROCEDURES

2.1. Information Required by Consumer Healthcare Research and Development for Regulatory Review

This study will not start in any country until the requirements of Consumer Healthcare Research and Development and all regulatory requirements for the country in which the trial will be conducted have been satisfied. The following documents and information must be provided by the principal investigator to Consumer Healthcare Research and Development:

2.1.1. Prior to Study Initiation

2.1.1.1.New Product Application (IND)

Signed protocol (and amendments, if applicable);

A completed, signed FDA Statement of Investigator (FDA Form 1572) for each principal investigator and co-principal investigator;

Current curriculum vitae for the principal investigator, co-principal investigators, and subinvestigators listed on 1572s;

Current and dated laboratory reference ranges for any laboratory listed on 1572s;

Current and dated laboratory certifications for any laboratory listed on 1572s;

IRB or EC approvals of the study protocol; amendments, when applicable; ICDs; and advertisements used to recruit subjects, if applicable. IRB/EC approvals should include specific reference to document approved, the formal name of the IRB/EC issuing the approval, and the signature of the chairperson of the IRB/EC or designate. If the IRB/EC reviewed a specific outline or abridgment of the protocol prepared by the investigator instead of the complete protocol, a copy of the document actually reviewed should also be supplied to Consumer Healthcare Research and Development.

Signed clinical study agreement and

Institutional review board/ethics committee membership list.

2.1.1.2.Non - IND Application

- Signed protocol (and amendments, if applicable);
- IRB/EC approvals of the study protocol; amendments, when applicable; ICDs; and advertisements used to recruits study subjects, if applicable
- Regulatory approval of protocol (and amendments), if dictated by local law;
- Current curriculum vitae for each principal investigator and co-principal investigator ;
- Current laboratory reference ranges and certifications
- Signed clinical study agreement and
- Institutional review board/ethics committee membership list.

2.1.2. During the Study

Revisions or updates to any documents listed in Section 2.1.1;

Completed CRFs for each subject entered into the study;

All documents related to all serious adverse events and pregnancies and any reports to the IRB/EC describing serious adverse events or deaths either caused by or during use of the investigational drug; and

Investigator's annual progress report to the IRB/EC, and a copy of the annual IRB/EC reapproval of the study upon which the report is based, if dictated by local law.

2.1.3. End-of-Study

Further revisions or updates to any documents listed in Section 2.1.1;

Completed subject CRFs not yet retrieved;

Investigator's final report of the study, if applicable;

Investigator's written notification to IRB/EC regarding study completion or discontinuation, if dictated by local law;

Signed Statement of Clinical Study Close-Out;

Signed Investigator Authorization of Data Clarification Letter.

2.2. Document Storage and Retention

Warner-Lambert policy requires that, following completion of a clinical study, the Principal Investigator must maintain all study records, including source documents, until otherwise notified by Warner-Lambert.

RECORDS MAY NOT BE DESTROYED OR DISCARDED WITHOUT THE WRITTEN PERMISSION OF WARNER-LAMBERT COMPANY.

Each completed original CRF, dated and signed by the investigator, and any data clarification forms (DCFs), dated and signed by the investigator, will be returned promptly to Warner-Lambert. A copy of each completed CRF and DRF must be retained at the site.

In order to assure the accuracy of data collected in the CRFs, it is mandatory that representatives of Warner-Lambert Company have access to original source documents. Source documents include subject records, subject charts, study records/worksheets, laboratory reports, etc. During the review of these documents, the anonymity of the subject will be respected, with strict adherence to professional standards of confidentiality. Warner-Lambert Company reserves the right to terminate the study for refusal of the investigator to supply source documentation of work performance for this study.

2.3. Guidelines for Recording Data in the Case Report Forms

The completed CRF is a legal document as it may be intended for submission to a federal regulatory agency as part of a regulatory submission. Therefore, the following guidelines must be followed in its completion.

All data entered on the CRF must be in black or blue ink. No data entry in the original CRF may be deleted or corrected by either erasure, use of ink eradication fluid, liquid paper, adhesive correction tape, or any other means. When a data entry is in error, draw a single line through the erroneous entry (the original data must remain discernible) and indicate the correct data in whatever way is appropriate. All correction(s) with reason(s) for corrections (e.g., entry error) must be initialed and dated by one of the investigators or his/her designee. Usually the initials should be near the corrected data, clearly associated with the specific correction being made;

Validity of data recorded on CRFs during each subject visit will be attested to by a dated signature. As indicated on each CRF, some must be signed by an investigator, others can be signed by a study coordinator;

All questions should be answered. If information cannot be provided, appropriately enter or mark a single line; NA for Not Applicable/Available; ND for Not Done; or UNK for Unknown;

Each page of the CRF must contain the subject's initials, the subject's ID number, as well as the study number in the spaces provided. In the interest of subject privacy, initials rather than full names should be used for identification. For the same reason, the social security number, address, or home telephone number of a subject should not be entered in the CRF.

The investigator is responsible for providing the completed original CRF for each subject to the Consumer Healthcare Research and Development Site Monitor/Clinical Research Associate. If the subject is hospitalized, the information in the CRF may be compared with the subject's hospital records by the Consumer Healthcare Research and Development Site Monitor/Clinical Research Associate to verify its accuracy. If, because of institutional policy, only a copy of certain hospital records can be included in the CRF, the copy must be completely legible and either be signed or initialed in ink by the investigator. Since this verified copy will be considered as and dated the original by Consumer Healthcare Research and Development, the investigator is responsible for informing Consumer Healthcare Research and Development of any change that may be made in the "true" original that will be in the subject's hospital records.

2.4. Review of Case Report Forms

The completed CRFs will be reviewed by Consumer Healthcare Research and Development Medical/Dental Colleagues, Site Monitor/Clinical Research Associates, and Clinical Data Management, or equivalent persons in a designated Contract Research Organization. The investigator will be contacted if any corrections or additions are necessary. The investigator is responsible for cooperating fully with Consumer Healthcare Research and Development personnel or its designee in correcting any erroneous or contradictory data entries.

2.5. Investigator's Responsibility for Clinical Product Supply Accountability

All clinical product supplies, i.e., new or marketed product, any corresponding placebo, and any active product control (including marketed formulations) in finished dosage form, provided by Consumer Healthcare Research and Development to the investigator for use in the clinical study must be accounted for in written documentation (i.e., records of receipt, dispensing, and return/destruction) that must be maintained and retained by the investigator and that will be monitored by Consumer Healthcare Research and Development personnel. Note: if applicable, the investigator may designate a pharmacist to be responsible for clinical product supply accountability.

2.5.1. Receipt of Clinical Product Supplies

The investigator must verify and acknowledge the receipt of clinical product supplies and retain related documentation.

2.5.2. Storage

Product drug supplies must be maintained as specified in the protocol (e.g., environmental conditions required for stability) under secure (locked) conditions. Access to the stored study product should be limited to the investigators, the study coordinator, and the pharmacist (when applicable).

2.5.3 Dispensing of Clinical Product Supplies

Product Dispensing records must be maintained. The investigator must assure completion of the product dispensing records with appropriate information (e.g., amount dispensed and returned by the subject, etc). The product dispensing records must be retained by the investigator along with the subject's study records.

2.5.4. Return of Clinical Product Supplies

As specified in the protocol, all product containers and all unused products remaining at the termination or completion of the study must be returned to the address shown in the protocol or with the product shipment.

Used product containers should be maintained separately and returned periodically during the trial. The Consumer Healthcare Research and Development Site Monitor/Clinical Research Associate will assist in returning product and containers as required. The investigator must document on appropriate forms the quantity of containers returned. All returned products provided by Consumer Healthcare Research and Development will be counted by Clinical and Consumer Packaging Operations or designee.

When applicable, any on-site product destruction must be pre-approved by Consumer Healthcare Research and Development, and actual product destruction must be documented.

3. PROTOCOL AMENDMENTS AND ADDENDA

Definitions

A *protocol amendment* is any systematic change (e.g., revision, addition, deletion) that is made to the Final Protocol for all sites from a clinical study and is identified by consecutive Arabic numerals (e.g., Amendment 1, Amendment 2, etc). Amendments can be made regardless of whether the protocol has been signed by the investigator or whether or not the protocol has been implemented at a site.

An *Urgent Protocol Amendment* is one that must be instituted quickly, usually to eliminate an apparent immediate hazard to subjects and may be implemented prior to eventual IRB/EC review (within 5 working days) and submission to regulatory authorities.

The principal investigator, Study Monitor/CRA working on the study and the senior member of each of the following departments or their designee, must approve all amendments to the protocol: Medical/Dental Affairs, Statistics & Data Management, and Regulatory Affairs. The VP Medical/Clinical Research and Development Affairs/ VP Oral Care, may sign if deemed appropriate. The investigator is responsible for submitting any proposed change in the approved protocol in writing to the IRB/EC for review and approval and for sending a copy of the approval to Consumer Healthcare Research and Development. The Regulatory Affairs Departments of Consumer Healthcare Research and Development will file all amendments to studies that have been filed with a regulatory agency with the FDA or appropriate regulatory authorities.

With the exception indicated in Section 3.1 below, the amendment/addendum will apply to all subjects entered into the study (or all subjects in affected sites for addenda) after it has gone through the applicable procedure described above and been approved by the IRB/EC. Any amendments proposed in a multicenter protocol must be approved by the IRB/EC at the individual study site before it can be placed in effect at that site.

Protocol modifications or amendments fall into one of the following categories.

3.1. Urgent Protocol Amendment

If the amendment eliminates an apparent immediate safety hazard to the subject (urgent protocol amendment), it may be implemented immediately. Consumer Healthcare Research and Development will promptly notify the FDA and/or appropriate regulatory

authorities of the amendment while the investigator will notify his/her IRB/EC of the change in writing within 5 working days of its implementation.

3.2. Other Amendments

Examples of protocol modifications requiring amendments to the Final Protocol and thus prior IRB/EC approval include:

- Changes in the drug dosage or formulation;
- Increases in subjects'/subjects' duration of exposure to drug;
- Increases in subject numbers;
- Significant changes in protocol design (e.g., drop/add control group)
- Addition of a test/procedure that better monitors/reduces risk of side effects/adverse events;
- Elimination of test intended to monitor safety;
- Specific request from a regulatory agency;
- Modification in entry (ie, inclusion/exclusion) or evaluability criteria;
- Significant change in safety/efficacy status of the clinical test product;
- Ambiguity (scientific or grammatical) in the protocol that needs clarification;

3.3. Study Termination

Warner Lambert Company may terminate the Study at any time in the exercise of its sole discretion upon fifteen- (15) days prior written notice to Institution. The Study may be terminated by Institution upon fifteen- (15) days prior written notice to Warner because of significant subject safety concerns or for other material and significant reasons. Upon receipt or giving of notice, as the case may be, Institution agrees to promptly terminate conduct of the Study to the extent medically permissible for all subjects. In the event of termination hereunder, other than as a result of a material breach by Institution, the total sums payable by Warner pursuant to this Agreement shall be equitably pro-rated for actual work performed to the date of termination with any unexpended funds previously paid by Warner to Institution being refunded to Warner.

3.4. Deviations from Protocol

A copy of the approved protocol will be kept on file at Warner-Lambert Company and the study site. Neither the investigator nor the sponsor are permitted to deviate from the protocol.

Apart from regulatory requirements, it is vital to the success of the study that the investigator adheres to the details of the protocol and thus, holds to a minimum the number of cases later classified as 'incomplete' or 'unusable.'

When a situation occurs that requires departure from the protocol, the investigator will contact the study monitor. Contact with the study monitor will be made as soon as possible in order to discuss the situation and to agree on an appropriate course of action.

Warner-Lambert Company reserves the right not to compensate the investigator for evaluation of cases in which the procedures and evaluations are conducted in a manner other than that specified by the protocol.

APPENDIX D
The Declaration of Helsinki

The Declaration of Helsinki

Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects

Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964,

and amended by
the 29th World Medical Assembly, Tokyo, Japan, October 1975;
the 35th World Medical Assembly, Venice, Italy, October 1983;
the 41st World Medical Assembly, Hong Kong, September 1989;

and the

48th General Assembly, Somerset West, Republic of South Africa, October 1996

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INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my subject will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the subject's interest when providing medical care which might have the effect of weakening the physical and mental condition of the subjects."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic, and prophylactic procedures and the understanding of the etiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic, or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a subject, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil, and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

A. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

B. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment, and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

C. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

D. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

E. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

F. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

G. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

H. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

I. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits, and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

J. When obtaining informed consent for the research project, the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be

obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

K. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation

Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

L. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (CLINICAL RESEARCH)

A. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health, or alleviating suffering.

B. The potential benefits, hazards, and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

C. In any medical study, every subject - including those of a control group, if any - should be assured of the best-proven diagnostic and therapeutic methods. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

D. The refusal of the subject to participate in a study must never interfere with the physician-subject relationship.

E. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee.(I,B)

F. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the subject.

III. NONTHERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (NON-CLINICAL BIOMEDICAL RESEARCH)

A. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

B. The subjects should be volunteers - either healthy persons or subjects for whom the experimental design is not related to the subject's illness.

C. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.

D. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

APPENDIX E
STUDY SAFETY PROCEDURES

Oral Tissue Assessment: Buccal, labial and sublingual mucosae, tongue, hard and soft palate, uvula and oropharynx, and teeth will be examined at screening, and every clinic visit. Aberrations will be recorded (Appendix G- Oral Tissue Assessment CRF), their severity assessed and a judgment made as to whether they can be attributable to the test materials.

"Aberrations" may include, but are not limited to cheek bites, food burns, mechanical trauma such as toothbrush or floss abrasions, amalgam tattoos, bony exostoses, geographic tongue, corrugated tongue, Fordyce granules, linea alba, traumatic ulcers, aspirin burns, tooth and restoration fractures and extrinsic tooth stain. Such conditions will typically be recorded as soft tissue abnormalities and not as adverse events.

An expected outcome for some subjects may be a transient burning or tingling sensation on the oral soft tissues, which has been reported with use of essential oil containing products. If there is no clinical aberration in those subjects reporting this sensation, then it will not be considered an adverse event and the comment will be captured by the subject on his/her diary, and/or as a comment on a clinical CRF. All other oral complaints require a clinical evaluation and diagnosis to be recorded as an adverse event.

Follow-up will be conducted until condition returns to normal or up to 30 days.

APPENDIX F

CASE REPORT FORM

I. SCREENING PROCEDURES

Date:_____Examiner:_____

Demographic data

Subject's initial_____Subject's number_____
Race _____Date of Birth _____
Sex Male Female Smoker Yes No

General and Oral Health Screening

Informed Consent: **Yes** No
Medical History Information Provided: **Yes** No (use attached forms)
Pre-medication for dental procedure: Yes **No**
General Health Condition: **Pass** Fail
Fluoridated Water Supply: **Yes** No
Other Fluoride Supplements Yes **No**
Wearing removable partial denture: **Yes** No
Oral Examination: **Yes** No (use oral soft tissue exam form)
Oral Health Condition: **Pass** Fail

History of allergic or idiosyncratic reaction to oral hygiene products:

Yes **No**

Subject accepted: **Yes** No
If not, explain:_____
_____

Written Instructions Provided: **Yes** No
Dental Prophylaxis **Yes** No
Product Distribution:

Toothbrush **Yes** No
Non-fluoride toothpaste **Yes** No
Mouthrinse **Yes** No

Examiner's Signature_____ Date _____

CASE REPORT FORM

II. ORAL SOFT TISSUE EXAM

Subject's Initials _____ Subject's No. _____

Visit Number: _____ Date of Exam_____

Condition of:	Normal	Describe abnormality
lips	_____	_____
buccal mucosa	_____	_____
labial mucosa	_____	_____
sublingual mucosa	_____	_____
attached gingivae	_____	_____
tongue	_____	_____
hard/soft palate	_____	_____
uvula	_____	_____
oropharynx	_____	_____
teeth	_____	_____
other	_____	_____

Abnormality attributable to experimental oral rinses? Yes _____No _____NA _____

Comments:

Examiner's Signature _____Date_____